

REMARKS/ARGUMENTS

Upon entry of this amendment, claims 42 and 45-56 are pending in this application and are presented for examination. Claims 1-41 and 43-44 have been canceled without prejudice to future prosecution. Claims 42 and 45-47 have been amended. Claims 53-56 are newly added.

Support for the amendments to the claims is found, for example, on page 5, lines 27-34; on page 6, lines 13-21; from page 18, line 36 to page 19, line 7; in Table 1 on page 51 (GRO3 and HNL); in Table 1 on page 55 (MMP-12 and elafin); and in Table 1 on page 56 (COL6A3) of the instant specification. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

I. SPECIFICATION OBJECTION

The Examiner has objected to the specification as allegedly failing to comply with the requirements for a Sequence Listing (*see*, Office Action at page 3).

In response, Applicant submits herewith a Substitute Sequence Listing and requests entry thereof in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the Substitute Sequence Listing, SEQ ID NOS:1-145, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter.

In view of the foregoing, Applicant respectfully requests withdrawal of the present objection and entry of the Substitute Sequence Listing.

II. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 42-52 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description and containing new matter. To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

A. Methods of Determining IBD

The Examiner alleges that the specification does not provide adequate support for the entire genus of methods of determining IBD or pre-IBD in a given tissue using the five claimed genes (*see*, Office Action at page 6). The Examiner also contends that part (a) of claim 42 constitutes new matter because the specification does not provide support for determining a single expression level based on a combination of the five claimed genes (*see*, Office Action at page 16). In response, Applicant asserts that the specification clearly demonstrates to one of skill in the art that the present inventor was in full possession of the claimed invention at the time of filing.

In order to expedite prosecution of the present case, Applicant has amended claim 42 to recite a method for determining whether a test colon cell has a UC or CD phenotype comprising determining the expression level of *each* of the following gene products in the test colon cell: GRO3, HNL, MMP-12, elafin, *and* COL6A3. The method further comprises comparing the expression level of *each* of these gene products to an expression level of the same gene product in a normal colon cell, associating an increase in the expression level of *any* of these gene products in the test colon cell relative to the normal colon cell with a UC phenotype, and associating an increase in the expression level of the MMP-12 *or* elafin gene product in the test colon cell relative to the normal colon cell with a CD phenotype.

Applicant asserts that the instant specification adequately describes the claimed method of determining a UC or CD phenotype in a test colon cell by determining, comparing, and associating the expression level of *each* of the five claimed gene products relative to a normal colon cell. In particular, the specification discloses that the claimed method is based on the finding that certain gene products are differentially expressed in the colonic tissue of UC or CD patients compared with normal colonic tissue (*see*, specification at page 5, lines 30-32; at page 6, lines 13-21; and at page 18, line 36 to page 19, line 7). Table 1 on pages 51-59 of the specification sets forth *each* gene product that was identified as over- or underexpressed in UC- or CD-derived colon cells relative to normal colon cells. Regarding the claimed gene products, Table 1 shows that overexpression of *any one of* GRO3, HNL, MMP-12, elafin, *or* COL6A3 in test colon cells relative to normal colon cells is associated with a UC phenotype. Table 1 also

shows that overexpression of *either* MMP-12 *or* elafin in test colon cells relative to normal colon cells is associated with a CD phenotype. As such, Applicant submits that the specification provides an adequate description of the entire genus of the method as presently claimed.

In view of the foregoing remarks, the disclosure of the instant specification is more than adequate to demonstrate to one of skill in the art that Applicant had possession of the presently claimed invention at the time the application was filed. Accordingly, Applicant respectfully requests withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

B. Nucleic acid probes

The Examiner alleges that the specification does not provide adequate support for the sequences of the nucleic acid probes on the array (*see*, Office Action at pages 6-7). In response, Applicant asserts that the specification clearly demonstrates to one of skill in the art that the present inventor was in full possession of the claimed invention at the time of filing.

Claim 49 recites an array comprising nucleic acid probes of 12-40 nucleotides in length that are complementary to and hybridize under high stringency conditions to the claimed gene products. As such, one of skill in the art would recognize that a nucleic acid probe present on the claimed array has a sequence which corresponds to the complement of a 12-40 nucleotide portion of a GRO3, HNL, MMP-12, elafin, or COL6A3 gene product and hybridizes under high stringency conditions to that portion of the gene product.

In the Amendment dated March 23, 2007, Applicant amended the specification to provide the appropriate corresponding sequence identifier (SEQ ID NO:) for each GenBank Accession number set forth in Table 1. The enclosed Substitute Sequence Listing includes sequences corresponding to each GenBank Accession number in accordance with the requirements of 37 C.F.R. §§1.821 to 1.825. As set forth in M.P.E.P. § 2163.07(b), "[r]eplacing the identified material incorporated by reference with the actual text is not new matter." The specification at page 59, lines 19-20 explicitly incorporates all cited publications by reference. All of the sequences submitted in the Substitute Sequence Listing correspond to those published

in GenBank at the time the present application was filed. Thus, the Substitute Sequence Listing introduces no new matter and is fully supported by the specification as filed.

Since the specification provides the nucleotide sequence of each claimed gene product, one of skill in the art would appreciate that Applicant was in full possession of the nucleic acid probes present on the claimed array. In fact, the specification discloses art-recognized techniques for analyzing the nucleotide sequence of each claimed gene product to design nucleic acid probes that can be used on the claimed array. For example, the specification discloses that the sequence of each claimed gene product can be processed using an alignment algorithm or program such as BLAST or FASTA to identify stretches of non-homologous sequence (*see*, specification at page 14, line 3 to page 15, line 10). Nucleic acid probes having a sequence complementary to a portion of the non-homologous sequence can then be designed, tested for hybridization under high stringency conditions, and bound to a suitable substrate (*see*, specification at page 3, lines 19-37 and at page 19, line 18 to page 20, line 3).

In view of the foregoing remarks, the disclosure of the instant specification is more than adequate to demonstrate to one of skill in the art that Applicant had possession of the presently claimed invention at the time the application was filed. Accordingly, Applicant respectfully requests withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 42-52 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The Examiner alleges that claim 42 lacks sufficient antecedent basis for the term "given tissue type" and that the term "pre-IBD phenotype" is indefinite (*see*, Office Action at page 15). The Examiner further alleges that it is unclear whether claim 42 recites alternative limitations for determining the expression level of the claimed genes (*see, id.*).

In order to expedite prosecution of the present case, Applicant has amended claim 42 to delete the terms "pre-IBD" and "given tissue type" from the claim. Applicant has also

amended claim 42 to clarify that the claimed method comprises determining the expression level of *each* of the following gene products in the test colon cell: GRO3, HNL, MMP-12, elafin, and COL6A3.

In view of the foregoing remarks, the claims are definite and claim the present invention with particularity. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

IV. REJECTION UNDER 35 U.S.C. § 102(e)

Claims 42-44, 46-48, and 50-52 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Cocks *et al.* (U.S. Patent No. 6,607,879). To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

For a rejection of claims under § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *see also, Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

The Examiner alleges that Cocks *et al.* teaches methods for diagnosing or monitoring diseases such as CD or UC using a microarray comprising cDNAs including GRO- γ (*i.e.*, GRO3) (*see*, Office Action at pages 17-18). In response, Applicant asserts that Cocks *et al.* fails to teach all of the elements of the claimed invention.

As discussed above, Applicant has amended claim 42 to recite a method for determining whether a test colon cell has a UC or CD phenotype comprising determining the

expression level of *each* of the following gene products in the test colon cell: GRO3, HNL, MMP-12, elafin, and COL6A3. Applicant asserts that Cocks *et al.* fails to teach or suggest the method of claim 42 in which the expression level of *each* of the five claimed gene products is determined. In fact, Cocks *et al.* does not teach or suggest determining the expression level of HNL, MMP-12, elafin, or COL6A3. As a result, Cocks *et al.* does not anticipate the presently claimed method because each and every element as set forth in claim 42 is not found in the reference. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection under 35 U.S.C. § 102(e).

V. REJECTION UNDER 35 U.S.C. § 103(a)

As set forth in M.P.E.P. § 2141 (I), the Patent Office's policy is to follow *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), in the consideration and determination of obviousness under 35 U.S.C. § 103. The four factual inquiries enunciated in *Graham* for determining obviousness are as follows:

- (A) Determining the scope and contents of the prior art;
- (B) Ascertaining the differences between the prior art and the claims in issue;
- (C) Resolving the level of ordinary skill in the pertinent art; and
- (D) Evaluating evidence of secondary considerations.

Recently, the U.S. Supreme Court affirmed the holding of *Graham* regarding obviousness. *See, KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007).

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. *See*, M.P.E.P. § 2143.

A. Alexander *et al.* in view of Poulakkainen *et al.*

Claims 42-48 and 50-52 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Alexander *et al.* (*Digestive Diseases and Sciences*, 41:660-669 (1996)) in

view of Poulakkainen *et al.* (*Gastroenterology*, 114:A1064 (1998)). To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The Examiner alleges that it would have been *prima facie* obvious for one of skill in the art to use all of the known genes involved in IBD in an array to determine an IBD or pre-IBD phenotype based on the teachings of Alexander *et al.* and Poulakkainen *et al.* (*see*, Office Action at page 10). In response, Applicant asserts that the presently claimed invention is not obvious in view of the cited art for at least the following reason: the combination of references does not teach or suggest all the elements of the presently claimed invention.

Applicant submits that the primary reference cited by the Examiner does not teach or suggest the presently claimed method of determining whether a test colon cell has a UC or CD phenotype comprising determining the expression level of *each* of the following gene products in the test colon cell: GRO3, HNL, MMP-12, elafin, *and* COL6A3. Rather, Alexander *et al.* discloses the differential expression of the protooncogenes H-*ras*, c-*myc*, c-*fos*, c-*jun*, *junB*, N-*myc*, c-*abl*, and c-*yes* in colonic epithelial cells of IBD patients. In fact, the Examiner has acknowledged that Alexander *et al.* does not specifically teach any of the claimed genes (*see*, Office Action at page 9).

However, the Examiner alleges that the genes listed in Table 1 of the instant specification, which includes the five claimed genes, are well known for their role in IBD (*see*, Office Action at pages 9-10). Contrary to the Examiner's allegation, Applicant asserts that the Examiner has improperly characterized the sequences disclosed in Table 1 as being well known for their role in IBD. Although these sequences were known in the art, Applicant submits that the differential expression of gene products such as COL6A3 was never appreciated to have a role in IBD until the advent of the present invention. In fact, the instant specification is the first to show that overexpression of *either* GRO3, HNL, MMP-12, elafin, *or* COL6A3 in test colon cells relative to normal colon cells is associated with a UC phenotype, while overexpression of *either* MMP-12 *or* elafin in test colon cells relative to normal colon cells is associated with a CD phenotype. As such, Applicant believes that the Examiner has impermissibly used an inventive feature of the claimed invention (*i.e.*, the discovery that the differential expression of *each* of the

five claimed gene products can be used in a method for determining whether a test colon cell has a UC or CD phenotype) in making this obviousness rejection.

The secondary reference cited by the Examiner fails to supply the teaching that is clearly lacking in Alexander *et al.* In particular, Applicant asserts that Poulakkainen *et al.* is completely silent regarding the presently claimed method of determining whether a test colon cell has a UC or CD phenotype comprising determining the expression level of *each* of the five claimed gene products in the test colon cell. Rather, this reference only describes the differential expression of MMP-10, MMP-13, MMP-12, and TIMP-3 in intestinal ulcerations.

Since neither of the references cited by the Examiner contemplates the presently claimed invention, it necessarily follows that the *combination* of these references fails to disclose or suggest all of the elements of the presently claimed invention. Importantly, these references, even when *combined*, lack any teaching or suggestion whatsoever regarding the claimed method of determining whether a test colon cell has a UC or CD phenotype comprising determining the expression level of *each* of the five claimed gene products in the test colon cell. At best, the *combined* disclosures of the cited references teaches the differential expression of *only one* of the five claimed gene products, MMP-12. Accordingly, the *combined* disclosures of Alexander *et al.* and Poulakkainen *et al.* do not render the claimed method obvious. Therefore, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

B. Dieckgraefe *et al.* in view of Puolakkainen *et al.*

Claims 42-52 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dieckgraefe *et al.* (*Gastroenterology*, 114:A964-965 (1998)) in view of Puolakkainen *et al.* To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The Examiner alleges that it would have been *prima facie* obvious for one of skill in the art to use all of the known genes involved in IBD in an array to determine an IBD or pre-IBD phenotype based on the teachings of Dieckgraefe *et al.* and Poulakkainen *et al.* (*see*, Office Action at page 13). In response, Applicant asserts that the presently claimed invention is not

obvious in view of the cited art for at least the following reason: the combination of references does not teach or suggest all the elements of the presently claimed invention.

Applicant submits that the primary reference cited by the Examiner does not teach or suggest the presently claimed method of determining whether a test colon cell has a UC or CD phenotype comprising determining the expression level of *each* of the following gene products in the test colon cell: GRO3, HNL, MMP-12, elafin, *and* COL6A3. Rather, Dieckgraefe *et al.* discloses an oligonucleotide probe array that detected changes in the expression of different classes of genes in IBD specimens, but without reference to any particular genes in those classes. In fact, Dieckgraefe *et al.* does not specifically teach or suggest any of the genes set forth in the presently claimed method.

Applicant respectfully reminds the Examiner that the sequences disclosed in Table 1 have been improperly characterized as being well known for their role in IBD. Although these sequences were known in the art, Applicant submits that the differential expression of gene products such as COL6A3 was never appreciated to have a role in IBD until the advent of the present invention. In fact, the instant specification is the first to show that overexpression of *either* GRO3, HNL, MMP-12, elafin, *or* COL6A3 in test colon cells relative to normal colon cells is associated with a UC phenotype, while overexpression of *either* MMP-12 *or* elafin in test colon cells relative to normal colon cells is associated with a CD phenotype. As such, Applicant believes that the Examiner has impermissibly used an inventive feature of the claimed invention (*i.e.*, the discovery that the differential expression of *each* of the five claimed gene products can be used in a method for determining whether a test colon cell has a UC or CD phenotype) in making this obviousness rejection.

The secondary reference cited by the Examiner fails to supply the teaching that is clearly lacking in Dieckgraefe *et al.* As discussed above, Poulakkainen *et al.* describes the differential expression of MMP-10, MMP-13, MMP-12, and TIMP-3 in intestinal ulcerations, but is completely silent regarding the presently claimed method of determining whether a test colon cell has a UC or CD phenotype comprising determining the expression level of *each* of the five claimed gene products in the test colon cell.

Since neither of the references cited by the Examiner contemplates the presently claimed invention, it necessarily follows that the *combination* of these references fails to disclose or suggest all of the elements of the presently claimed invention. Importantly, these references, even when *combined*, lack any teaching or suggestion whatsoever regarding the claimed method of determining whether a test colon cell has a UC or CD phenotype comprising determining the expression level of *each* of the five claimed gene products in the test colon cell. At best, the *combined* disclosures of the cited references teaches the differential expression of *only one* of the five claimed gene products, MMP-12. Accordingly, the *combined* disclosures of Dieckgraefe *et al.* and Poulakkainen *et al.* do not render the claimed method obvious. Therefore, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

C. Alexander *et al.* in view of Poulakkainen *et al.* and Dieckgraefe *et al.*

Claims 42-52 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Alexander *et al.* in view of Poulakkainen *et al.* and Dieckgraefe *et al.* To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The Examiner alleges that it would have been *prima facie* obvious for one of skill in the art to use probes having a specified length to detect the expression of gene products based on the teachings of Alexander *et al.*, Poulakkainen *et al.*, and Dieckgraefe *et al.* (*see*, Office Action at page 19). In response, Applicant asserts that the presently claimed invention is not obvious in view of the cited art for at least the following reason: the combination of references does not teach or suggest all the elements of the presently claimed invention.

As discussed above, none of the references cited by the Examiner teaches or suggests the presently claimed method of determining whether a test colon cell has a UC or CD phenotype comprising determining the expression level of *each* of the following gene products in the test colon cell: GRO3, HNL, MMP-12, elafin, and COL6A3. Since none of these references contemplates the presently claimed invention, it necessarily follows that the *combination* of these references fails to teach or suggest all of the elements of the presently claimed invention. In fact, even when these references are *combined*, there remains a lack of any teaching or suggestion whatsoever regarding the presently claimed method of determining the expression level of *each*

of the five claimed gene products. At best, the *combined* disclosures of the cited references teaches the differential expression of *only one* of the five claimed gene products, MMP-12. Accordingly, the *combined* disclosures of Alexander *et al.*, Poulakkainen *et al.*, and Dieckgraefe *et al.* do not render the claimed method obvious. In view of the foregoing remarks, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

D. Cocks *et al.* in view of Alexander *et al.* and Dieckgraefe *et al.*

Claims 42-52 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Cocks *et al.* in view of Alexander *et al.* and Dieckgraefe *et al.* To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The Examiner alleges that it would have been *prima facie* obvious for one of skill in the art to use probes having a specified length to detect the expression of gene products for distinguishing between UC and CD based on the teachings of Cocks *et al.*, Alexander *et al.*, and Dieckgraefe *et al.* (*see*, Office Action at page 20). In response, Applicant asserts that the presently claimed invention is not obvious in view of the cited art for at least the following reason: the combination of references does not teach or suggest all the elements of the presently claimed invention.

As discussed above, none of the references cited by the Examiner teaches or suggests the presently claimed method of determining whether a test colon cell has a UC or CD phenotype comprising determining the expression level of *each* of the following gene products in the test colon cell: GRO3, HNL, MMP-12, elafin, *and* COL6A3. Since none of these references contemplates the presently claimed invention, it necessarily follows that the *combination* of these references fails to teach or suggest all of the elements of the presently claimed invention. In fact, even when these references are *combined*, there remains a lack of any teaching or suggestion whatsoever regarding the presently claimed method of determining the expression level of *each* of the five claimed gene products. At best, the *combined* disclosures of the cited references teaches the differential expression of *only one* of the five claimed gene products, GRO3. Thus, the *combined* disclosures of Cocks *et al.*, Alexander *et al.*, and Dieckgraefe *et al.* do not render

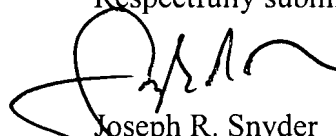
the claimed method obvious. Accordingly, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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